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(54) Title: USE OF THIAZOLIDINEDIONE DERIVATIVES AND RELATED ANTIHYPERGLYCEMIC AGENTS IN THE TREATMENT OF DISEASE STATES AT RISK FOR PROGRESSING TO NONINSULIN-DEPENDENT DIABETES MELLITUS		
(57) Abstract Novel methods of using thiazolidinone derivatives and related antihyperglycemic agents to treat populations at risk for developing noninsulin-dependent diabetes mellitus (NIDDM) and complications arising therefrom are disclosed. In one embodiment, the compounds of the invention are used to treat polycystic ovary syndrome in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus. In another embodiment, the compounds of the invention are used to treat gestational diabetes in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus.		

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USE OF THIAZOLIDINEDIONE DERIVATIVES AND RELATED
ANTIHYPERGLYCEMIC AGENTS IN THE TREATMENT OF
DISEASE STATES AT RISK FOR PROGRESSING TO
NONINSULIN-DEPENDENT DIABETES MELLITUS

5

FIELD OF THE INVENTION

10 The present invention pertains to a number of
compounds which can be used to treat certain disease
states in order to prevent or delay the onset of
noninsulin-dependent diabetes mellitus (NIDDM). More
specifically, the present invention involves in one
embodiment administering to a patient certain known
15 thiazolidinedione derivatives and related
antihyperglycemic agents which treat disease states
such as polycystic ovary and gestational diabetes
syndrome which are at increased risk in the development
of NIDDM, thus preventing or delaying the onset of
20 NIDDM or complications resulting therefrom.

BACKGROUND OF THE INVENTION

25 Diabetes is one of the most prevalent chronic
disorders worldwide with significant personal and
financial costs for patients and their families, as
well as for society. Different types of diabetes exist
with distinct etiologies and pathogeneses. For
30 example, diabetes mellitus is a disorder of
carbohydrate metabolism, characterized by hyperglycemia
and glycosuria and resulting from inadequate production
or utilization of insulin.

35 NIDDM, or otherwise referred to as Type II
diabetes, is the form of diabetes mellitus which occurs
predominantly in adults in whom adequate production of

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insulin is available for use, yet a defect exists in insulin-mediated utilization and metabolism of glucose in peripheral tissues. Overt NIDDM is characterized by three major metabolic abnormalities: resistance to
5 insulin-mediated glucose disposal, impairment of nutrient-stimulated insulin secretion, and overproduction of glucose by the liver. It has been shown that for some people with diabetes a genetic predisposition results in a mutation in the gene(s)
10 coding for insulin and/or the insulin receptor and/or insulin-mediated signal transduction factor(s), thereby resulting in ineffective insulin and/or insulin-mediated effects thus impairing the utilization or metabolism of glucose.

15 Reports indicate that insulin secretion is often enhanced early-on, presumably as compensation for the insulin resistance. People who actually develop NIDDM appear to do so because their B-cells eventually fail to maintain sufficient insulin secretion to compensate
20 for the insulin resistance. Mechanisms responsible for the B-cell failure have not been identified, but may be related to the chronic demands placed on the B-cells by peripheral insulin resistance and/or to the effects of hyperglycemia to impair B-cell function. The B-cell
25 failure could also occur as an independent, inherent defect in "pre-diabetic" individuals.

NIDDM often develops from certain at risk populations, one such population is individuals with polycystic ovary syndrome (PCOS). PCOS is the most
30 common endocrine disorder in women of reproductive age. This syndrome is characterized by hyperandrogenism and disordered gonadotropin secretion producing oligo- or anovulation. Recent prevalence estimates suggest that
35 5-10% of women between 18-44 years of age (about 5 million women, according to the 1990 census) have the full-blown syndrome of hyperandrogenism, chronic

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anovulation, and polycystic ovaries. Despite more than 50 years since its original description, the etiology of the syndrome remains unclear. The biochemical profile, ovarian morphology, and clinical features are non-specific; hence, the diagnosis remains one of exclusion of disorders, such as androgen-secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia.

PCOS is associated with profound insulin resistance resulting in substantial hyperinsulinemia. As a result of their insulin resistance, PCOS women are at increased risk to develop NIDDM. Hirsutism, acne, and alopecia, which are commonly found in PCOS women, are clinical manifestations of hyperandrogenism. Menstrual disturbances and infertility are the result of ovulatory dysfunction related to the disordered gonadotropin secretion. Androgen excess, probably by eventual conversion of androgens to estrogen, also plays an important role in disrupting gonadotropin release in PCOS.

There are two leading hypotheses for the association between PCOS and insulin resistance: 1) androgens produce insulin resistance or 2) hyperinsulinemia produces hyperandrogenism. In support of the first hypothesis, synthetic androgen administration can increase insulin levels in women. However, in PCOS women with acanthosis nigricans (which is a marker for insulin resistance), oophorectomy lowers testosterone levels but does not alter insulin resistance. Further, long-acting GnRH agonist treatment in PCOS women decreases plasma testosterone and androstenedione levels into the normal female range, but does not alter glucose tolerance, insulin levels, or insulin action. Thus, although certain synthetic androgens may have a modest effect on insulin sensitivity, natural androgens

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do not produce insulin resistance of the magnitude found in PCOS.

In contrast, there are several lines of evidence that support the alternative hypothesis that hyperinsulinemia produces hyperandrogenism. First, extreme insulin resistance of a variety of etiologies, ranging from insulin receptor mutations to autoimmune insulin resistance, is associated with ovarian hyperandrogenism. Second, insulin can directly stimulate ovarian androgen secretion in vitro and in vivo in PCOS women. Finally, decreasing insulin levels for 10 days with diazoxide results in a significant decrease in testosterone levels in PCOS women. Insulin does not alter gonadotropin release but rather appears to act directly on the ovary. However, these actions of insulin are not observed in normal ovulatory women, suggesting that polycystic ovarian changes are necessary for such insulin effects to be manifested.

Insulin resistance in PCOS is secondary to a marked decrease in insulin receptor-mediated signal transduction and a modest, but significant, decrease in adipocyte GLUT4 content. In many PCOS women, the decrease in insulin receptor signaling is the result of intrinsic abnormalities in insulin receptor phosphorylation. The magnitude of insulin resistance in PCOS is similar to that in NIDDM and in obesity. However, the cellular mechanisms of insulin resistance appear to differ in PCOS compared to these other common insulin-resistant states. The shift to the right in the insulin dose-response curve for adipocyte glucose uptake is much more striking in PCOS than in obesity. Further, decreases in adipocyte insulin sensitivity and responsiveness are significantly correlated with hyperinsulinemia, glycemia, and/or obesity in individuals with NIDDM or obesity, whereas insulin resistance is independent of these parameters in PCOS.

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Finally, no persistent abnormalities in insulin receptor autophosphorylation have been identified in NIDDM or obesity.

5 NIDDM also develops from the at risk population of individuals with gestational diabetes mellitus (GDM). Pregnancy normally is associated with progressive resistance to insulin-mediated glucose disposal. In fact, insulin sensitivity is lower during late pregnancy than in nearly all other physiological conditions. The insulin resistance is thought to be mediated in large part by the effects of circulating hormones such as placental lactogen, progesterone, and cortisol, all of which are elevated during pregnancy. In the face of the insulin resistance, pancreatic B-cell responsiveness to glucose normally increases nearly 3-fold by late pregnancy, a response that serves to minimize the effect of insulin resistance on circulating glucose levels. Thus, pregnancy provides a major "stress-test" of the capacity for B-cells to compensate for insulin resistance.

20 Studies of insulin action and B-cell function during pregnancy indicate that, during the third trimester, women with mild-moderate GDM have the same degree of insulin resistance as do non-diabetic pregnant women. However, studies during the second trimester and after pregnancy indicate that women with GDM are somewhat insulin resistant compared to women who maintain normal glucose tolerance during pregnancy. Taken together, the available data indicate that pancreatic B-cells of women who develop GDM may encounter two types of insulin resistance: 1) mild-moderate, underlying, and perhaps genetic insulin resistance that is present even when the women are not pregnant; and 2) the marked, physiological (probably hormonally-mediated) insulin resistance that occurs during pregnancy in all women. Data indicate that the

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main feature which distinguishes women with GDM from normal pregnant women during the third trimester, when all women are insulin resistant, is pancreatic B-cell function. Most women develop GDM because their
5 pancreatic B-cells are unable to maintain enhanced insulin secretion in the face of insulin resistance. That inability is very similar to the B-cell defect which has been observed in longitudinal studies of patients who develop NIDDM, a fact which may explain
10 why women with GDM are at such high risk for NIDDM: GDM identifies women whose B-cells will decompensate when faced with severe or chronic insulin resistance.

Other populations thought to be at risk for developing NIDDM are persons with Syndrome X; persons
15 with concomitant hyperinsulinemia; persons with insulin resistance characterized by hyperinsulinemia and by failure to respond to exogenous insulin; and persons with abnormal insulin and/or evidence of glucose disorders associated with excess circulating
20 glucocorticoids, growth hormone, catecholamines, glucagon, parathyroid hormone, and other insulin-resistant conditions.

Failure to treat NIDDM can result in mortality due to cardiovascular disease and in other diabetic
25 complications including retinopathy, nephropathy, and peripheral neuropathy. For many years treatment of NIDDM has involved a program aimed at lowering blood sugar with a combination of diet and exercise. Alternatively, treatment of NIDDM involved oral
30 hypoglycemic agents, such as sulfonylureas alone or in combination with insulin injections. Recently, alpha-glucosidase inhibitors, such as acarbose, have been shown to be effective in reducing the postprandial rise in blood glucose (Lefevre, et al., Drugs 1992;44:
35 29-38). In Europe and Canada another treatment used primarily in obese diabetics is metformin, a biguanide.

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In any event, what is required is a method of treating at risk populations such as those with PCOS and GDM in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders of the populations at risk for NIDDM. The methods of using the disclosed compounds for treating at risk populations with conditions such as PCOS and GDM to prevent or delay the onset of NIDDM as taught herein meet these objectives.

The compounds of the present invention, and methods of making the compounds, are known and some of these are disclosed in U.S. Patents 5,223,522 issued June 29, 1993; 5,132,317 issued July 12, 1992; 5,120,754 issued June 9, 1992; 5,061,717 issued October 29, 1991; 4,897,405 issued January 30, 1990; 4,873,255 issued October 10, 1989; 4,687,777 issued August 18, 1987; 4,572,912 issued February 25, 1986; 4,287,200 issued September 1, 1981. The compounds disclosed in these issued patents are useful as therapeutic agents for the treatment of diabetes, hyperglycemia, hypercholesterolemia, and hyperlipidemia. The teachings of these issued patents are incorporated herein by reference.

Regarding prevention of NIDDM, there has been one disclosure of this concept using a sulfonylurea as a treatment, but this concept is not highly regarded in the scientific community because prolonged treatment with sulfonylureas can reduce insulin secretion by destroying the pancreatic beta cells. Moreover, sulfonylureas can cause clinically severe hypoglycemia. The concept of using a biguanide, such as metformin, has also been disclosed.

There is no disclosure in the above-identified references to suggest the use of the compounds

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identified in this present application in the treatment of at risk populations such as those with PCOS or GDM in order to prevent or delay the onset of NIDDM and complications resulting therefrom.

5

SUMMARY OF THE INVENTION

10 In one embodiment of this invention, a method is disclosed for the treatment of PCOS in order to prevent or delay the onset of NIDDM. Improvement in insulin sensitivity by treatment with the compounds of the following formulas will reduce fasting insulin levels, thereby resulting in decreased androgen production and
15 biologic availability in PCOS women. Decreasing androgen levels will improve the clinical symptoms of androgen excess and the anovulation commonly found in PCOS women.

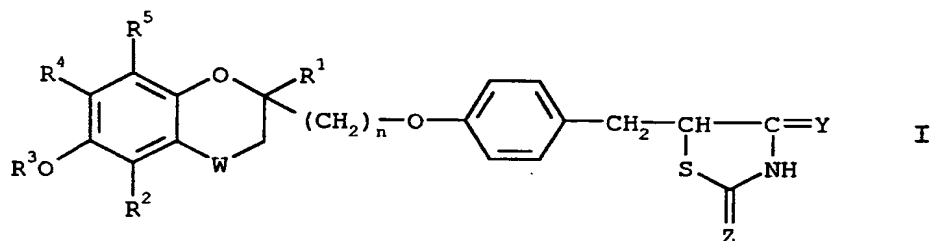
20 In another embodiment of this invention, a method is disclosed for the treatment of GDM. Improvement in whole-body insulin sensitivity by treatment with the compounds of the following formulas will reduce the rate of B-cell decomposition and delay or prevent the development of NIDDM in women with GDM. The compounds
25 can also be applied to former gestational diabetic women to delay or prevent NIDDM and its long-term complications. As agents having the aforementioned effects, the compounds of the following formulas are useful in treating individuals to prevent or delay the
30 onset of NIDDM.

In another embodiment of the present invention is a method for treating population states, other than those with PCOS or GDM, who are at risk for developing NIDDM. Other populations thought to be at risk for
35 developing NIDDM are persons with Syndrome X; persons with concomitant hyperinsulinemia; persons with insulin

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resistance characterized by hyperinsulinemia and by failure to respond to exogenous insulin; and persons with abnormal insulin and/or evidence of glucose disorders associated with excess circulating glucocorticoids, growth hormone, catecholamines, glucagon, parathyroid hormone, and other insulin-resistant conditions. Treatment of the above populations with the compounds of the following formulas will prevent or delay the onset of NIDDM.

Accordingly, the present invention is the use of compounds of Formula I



herein R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1 - C_6 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylenedioxy group;

n is 1, 2, or 3;

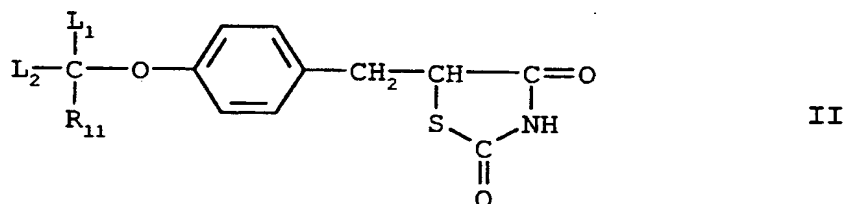
W represents the $-CH_2-$, $>CO$, or $CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino ($=NH$) group;

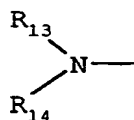
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and pharmaceutically acceptable salts thereof.

The present invention is also the use of compounds of the Formula II



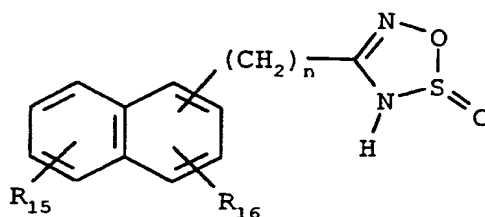
10 wherein R_{11} is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula



25 wherein R_{13} and R_{14} are the same or different and each is lower alkyl or R_{13} and R_{14} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring; wherein R_{12} means a bond or a lower alkylene group; and wherein L_1 and L_2 are the same or different and each is hydrogen or lower alkyl or L_1 and L_2 are combined to form an alkylene group; or a pharmaceutically acceptable salt thereof.

30 The present invention is also the use of compounds of the Formula III

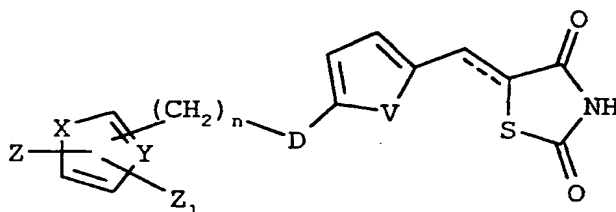
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III

wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

The present invention is also directed to the use of compounds of the Formula IV



IV

wherein the dotted line represents a bond or no bond;

V is $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-$ or S;

D is CH_2 , CHOH , CO , $\text{C}=\text{NOR}_{17}$ or $\text{CH}=\text{CH}$;

X is S, O, NR_{18} , $-\text{CH}=\text{N}$ or $-\text{N}=\text{CH}$;

Y is CH or N;

Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7) cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are (C_1-C_3) alkyl, trifluoromethyl,

(C_1-C_3) alkoxy, fluoro, chloro, or bromo;

Z_1 is hydrogen or (C_1-C_3) alkyl;

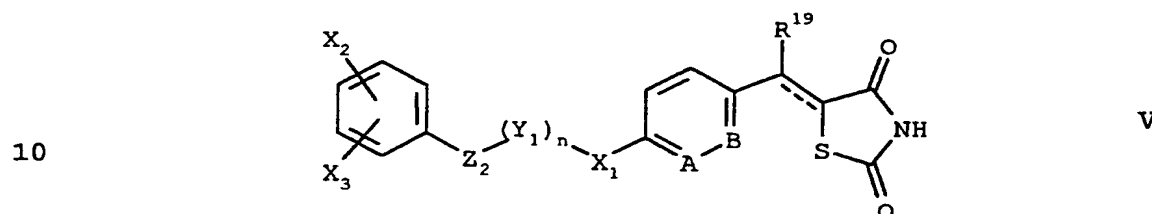
R_{17} and R_{18} are each independently hydrogen or methyl;

and n is 1, 2, or 3;

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the pharmaceutically acceptable cationic salts thereof;
and the pharmaceutically acceptable acid addition salts
thereof when the compound contains a basic nitrogen.

The present invention is also directed to the use
of compounds of the Formula V



wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the
proviso that when A or B is N, the other is CH;
X₁ is S, SO, SO₂, CH₂, CHOH, or CO;
n is 0 or 1;
Y₁ is CHR₂₀ or R₂₁, with the proviso that when n is 1
and Y₁ is NR₂₁, X₁ is SO₂ or CO;

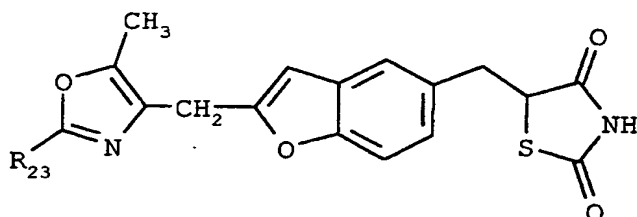
20 Z₂ is CHR₂₂, CH₂CH₂, CH=CH, $\text{CH}-\underset{\text{O}}{\text{CH}}$, OCH₂,

SCH₂, SOCH₂ or SO₂CH₂;
R₁₉, R₂₀, R₂₁, and R₂₂ are each independently hydrogen
or methyl; and

25 X₂ and X₃ are each independently hydrogen, methyl,
trifluoromethyl, phenyl, benzyl, hydroxy, methoxy,
phenoxy, benzyloxy, bromo, chloro, or fluoro;
a pharmaceutically acceptable cationic salt thereof; or
30 a pharmaceutically acceptable acid addition salt
thereof when A or B is N.

The present invention also relates to the use of
compounds of the Formula VI

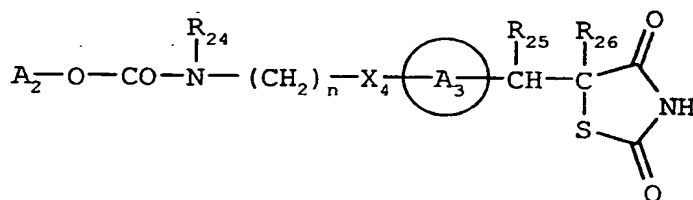
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VI

or a pharmaceutically acceptable salt thereof wherein R_{23} is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl or mono- or di-substituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

The present invention also provides the use of a compound of Formula VII



VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A_3 represents a benzene ring having in total up to 3 optional substituents;

R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the

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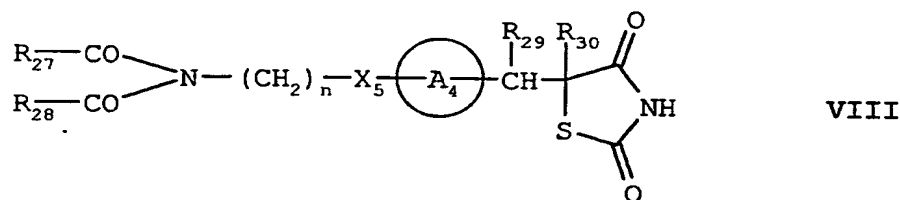
polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

5 R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;

X_4 represents O or S; and

n represents an integer in the range of from 2 to 6.

10 The present invention also provides the use of a compound of Formula VIII



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

20 R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety; or R_{27} together with R_{28}

25 represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-, aryl, 30 or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

35 R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30} together represent a bond;

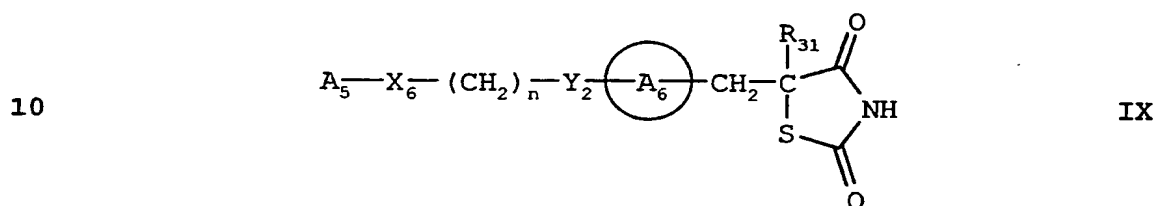
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A_4 represents a benzene ring having in total up to 3 optional substituents;

X_5 represents O or S; and

n represents an integer in the range of from 2 to 6.

5 The present invention also provides the use of a compound of Formula IX



15 or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_5 represents a substituted or unsubstituted aromatic heterocyclyl group;

20 A_6 represents a benzene ring having in total up to 5 substituents;

X_6 represents O, S, or NR_{32} wherein R_{32} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or

25 unsubstituted aryl group;

Y_2 represents O or S;

R_{31} represents an alkyl, aralkyl, or aryl group; and n represents an integer in the range of from 2 to 6.

30 Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur, or nitrogen.

35 Favored aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic

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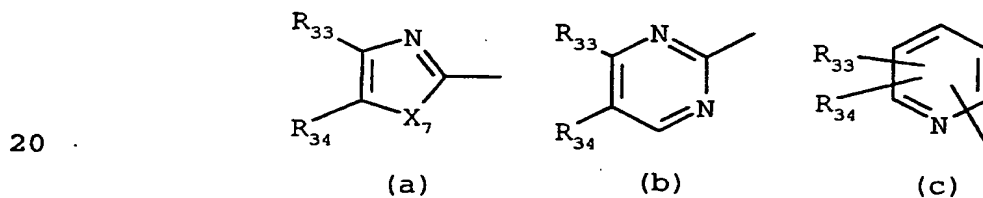
heterocyclyl groups having 4 to 7 ring atoms,
preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group
comprises 1, 2, or 3 heteroatoms, especially 1 or 2,
5 selected from oxygen, sulphur, or nitrogen.

Suitable values for A_5 when it represents a
5-membered aromatic heterocyclyl group include
thiazolyl and oxazolyl, especially oxazolyl.

Suitable values for A_5 when it represents a
10 6-membered aromatic heterocyclyl group include pyridyl
or pyrimidinyl.

Suitable R_{31} represents an alkyl group, in
particular a C_{1-6} alkyl group, for example a methyl
group. Preferably, A_5 represents a moiety of formula
15 (a), (b), or (c):

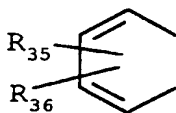


wherein:

25 R_{33} and R_{34} each independently represents a hydrogen
atom, an alkyl group, or a substituted or unsubstituted
aryl group or when R_{33} and R_{34} are each attached to
adjacent carbon atoms, then R_{33} and R_{34} together with
the carbon atoms to which they are attached form a
benzene ring wherein each carbon atom represented by
30 R_{33} and R_{34} together may be substituted or
unsubstituted; and in the moiety of Formula (a), X_7
represents oxygen or sulphur.

In one favored aspect R_{33} and R_{34} together
represent a moiety of Formula (d):

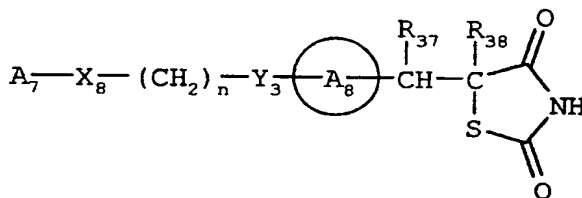
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(d)

wherein R_{35} and R_{36} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl, or alkoxy.

The present invention also provides for the use of compounds for Formula X



X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_7 represents a substituted or unsubstituted aryl group;

A_8 represents a benzene ring having in total up to 5 substituents;

X_8 represents O, S, or NR_{39} , wherein R_{39} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y_3 represents O or S;

R_{37} represents hydrogen;

R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and n represents an integer in the range of from 2 to 6.

A still further embodiment of the present invention is the use of a pharmaceutical composition

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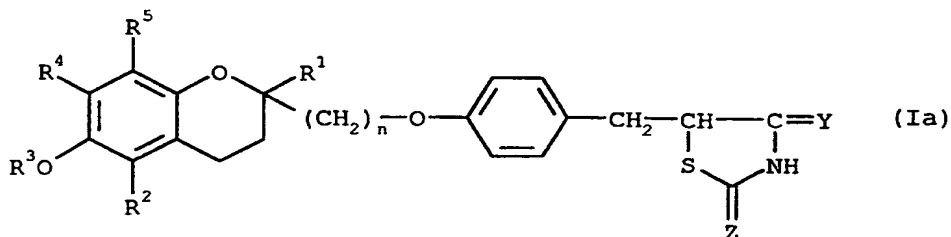
for administering an effective amount of a compound of the preceding Formulas I through X along with a pharmaceutically acceptable carrier in unit dosage form in the treatment methods mentioned above.

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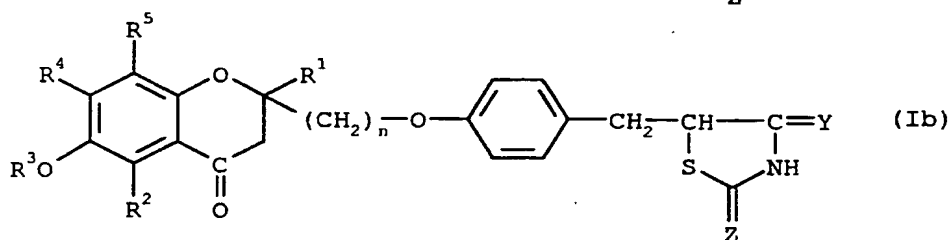
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compounds used in the treatment methods of the invention, which are 5-[4-(chromoanalkoxy)benzyl]-thiazolidene derivatives, may be represented by the Formulas (Ia), (Ib), and (Ic)

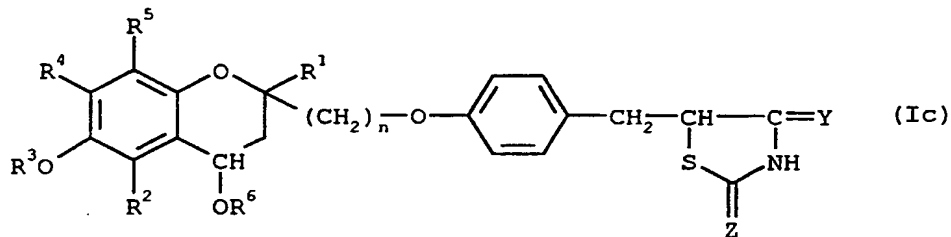
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(in which R¹, R², R³, R⁴, R⁵, R⁶, n, Y, and Z are as defined above) and include pharmaceutically acceptable salts thereof.

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In the compounds of the invention, where R^1 or R^2 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or isopentyl group.

Where R^3 , R^6 , or $R^{6'}$ represents an aliphatic acyl group, this preferably has from 1 to 6 carbon atoms and may include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl, and crotonyl groups.

Where R^3 , R^6 , or $R^{6'}$ represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl, or cycloheptanecarbonyl group.

Where R^3 , R^6 , or $R^{6'}$ represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such aromatic acyl groups included the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl, and 1-naphthoyl groups.

Where R^3 , R^6 , or $R^{6'}$ represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulfur, or nitrogen hetero atoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl (nicotinoyl), and 4-pyridinecarbonyl groups.

Where R^3 , R^6 , or $R^{6'}$ represents an araliphatic acyl group, the aliphatic moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or

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more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such araliphatic acyl groups include the phenylacetyl, p-chlorophenyl-
5 acetyl, phenylpropionyl, and cinnamoyl groups.

Where R^3 , R^6 , or $R^{6'}$ represents a (C_1 - C_6 alkoxy)carbonyl group, the alkyl moiety thereof may be any one of those alkyl groups as defined for R^1 and R^2 , but is preferably a methyl or ethyl group, and the
10 alkoxy carbonyl group represented by R^3 , R^6 , or $R^{6'}$ is therefore preferably a methoxycarbonyl or ethoxycarbonyl group.

Where R^3 , R^6 , or $R^{6'}$ represents an aralkyloxy-carbonyl group, the aralkyl moiety thereof may be any
15 one of those included within the araliphatic acyl group represented by R^3 , R^6 , or $R^{6'}$, but is preferably a benzyloxycarbonyl group.

Where R^4 and R^5 represent alkyl groups, they may be the same or different and may be straight or
20 branched chain alkyl groups. They preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and isopentyl groups.

Where R^4 and R^5 represent alkoxy groups, these may be the same or different and may be straight or
25 branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy, and butoxy groups. Alternatively, R^4 and R^5 may together represent a C_1 - C_4 alkylenedioxy group, more preferably a methylenedioxy or ethylene-
30 dioxy group.

Preferred classes of compounds of Formula I are as follows:

(1) Compounds in which R^3 represents a hydrogen
35 atom, a C_1 - C_6 aliphatic acyl group, an aromatic acyl group, or a heterocyclic acyl group.

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(2) Compounds in which Y represents an oxygen atom; R¹ and R² are the same or different and each represents a hydrogen atom or a C₁-C₅ alkyl group; R³ represents a hydrogen atom, a C₁-C₆ aliphatic acyl group, an aromatic acyl group, or a pyridinecarbonyl group; and R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁-C₅ alkyl group, or a C₁ or C₂ alkoxy group.

(3) Compounds as defined in (2) above, in which: R¹, R², R⁴, and R⁵ are the same or different and each represents a hydrogen atom or a C₁-C₅ alkyl group; n is 1 or 2; and W represents the -CH₂- or >CO group.

(4) Compounds as defined in (3) above, in which R³ represents a hydrogen atom, a C₁-C₅ aliphatic acyl group, a benzoyl group, or a nicotinyl group.

(5) Compounds as defined in (4) above, in which: R¹ and R⁴ are the same or different and each represents a C₁-C₅ alkyl group; R² and R⁵ are the same or different and each represents the hydrogen atom or the methyl group; and R³ represents a hydrogen atom or a C₁-C₄ aliphatic acyl group.

(6) Compounds in which: W represents the -CH₂- or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R¹ and R⁴ are the same or different and each represents a C₁-C₄ alkyl group; R² and R⁵ are the same or different and each represents the hydrogen atom or the methyl group; and R³ represents a hydrogen atom or a C₁-C₄ aliphatic acyl group.

(7) Compounds as defined in (6) above, in which n is 1.

(8) Compounds as defined in (6) or (7) above, in which W represents the -CH₂- group.

Preferred compounds among the compounds of Formula I are those wherein:

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R¹ is a C₁-C₄ alkyl group, more preferably a methyl or isobutyl group, most preferably a methyl group;

5 R² is a hydrogen atom or a C₁-C₄ alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group;

10 R³ is a hydrogen atom, a C₁-C₄ aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl, or nicotiny group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group;

15 R⁴ is a hydrogen atom, a C₁-C₄ alkyl group or a C₁ or C₂ alkoxy group, preferably a methyl, isopropyl, t-butyl, or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group;

20 R⁵ is a hydrogen atom, a C₁-C₄ alkyl group or a C₁ or C₂ alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group, and most preferably a methyl group;

n is 1 or 2, preferably 1;

Y is an oxygen atom;

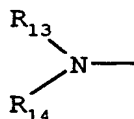
25 Z is an oxygen atom or an imino group, most preferably an oxygen atom; and

W is a -CH₂- or >C=O group, preferably a -CH₂- group.

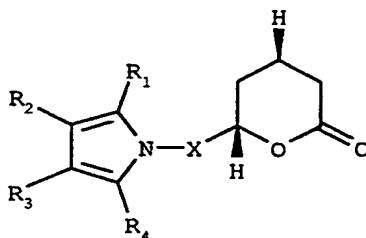
30 Referring to the general Formula II, the substituents may be any from 1 to 3 selected from nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy, the aromatic acyl group may be benzoyl and naphthoyl. The alkyl group R₁₁ may be a straight chain or branched alkyl of 1 to 10 carbon
35 atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl,

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n-heptyl, n-octyl, n-nonyl, and n-decyl; the cycloalkyl group R_{11} may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R_{11} may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R_{11} may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen, and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R_{11} is



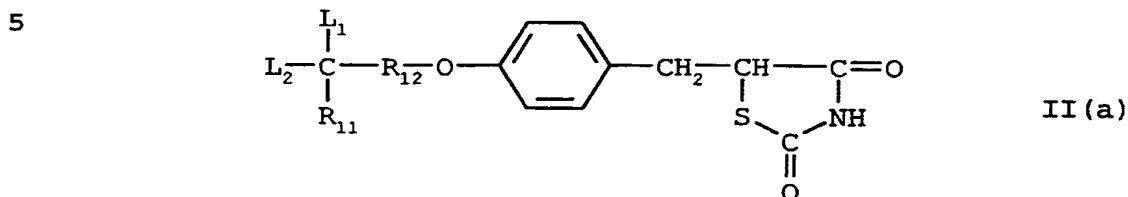
the lower alkyls R_{13} and R_{14} may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, and n-butyl. When R_{13} and R_{14} are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, i.e., in the form of



this heterocyclic group may further include a hetero-atom selected from among nitrogen, oxygen, and sulfur as exemplified by piperidino, morpholino, pyrrolidino, and piperazino. The lower alkylene group R_{12} may contain 1 to 3 carbon atoms and thus may be, for example, methylene, ethylene, or trimethylene. The bond R_{12} is equivalent to the symbol "-", ".", or the like which is used in chemical structural formulas, and

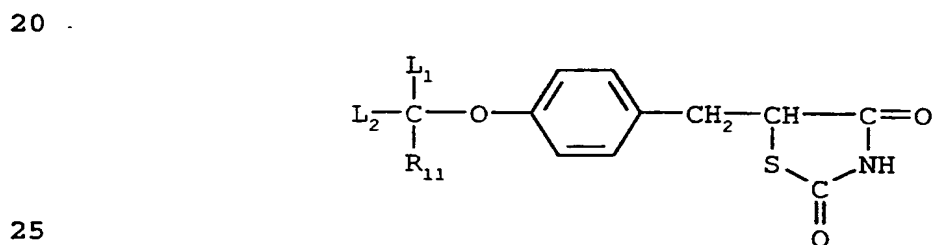
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when R_{12} represents such a bond, the compound of general Formula II is represented by the following general Formula II(a)



10 Thus, when R_{12} is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L_1 and L_2 , there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L_1 and L_2 are joined together is a group of the formula

15 $-(\text{CH}_2)_n-$ [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl, and heterocyclic groups mentioned above, as well as said heterocyclic group



may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.), and hydroxyl. The case also falls within the scope of the general Formula II that an alkylenedioxy group of the formula $-(\text{CH}_2)_m-\text{O}-$ [is an integer of 1 to 3], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

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The preferred compounds of Formula III are those wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, trifluoromethyl, vinyl, or nitro; n is 1 or 2 and the pharmaceutically acceptable salts thereof.

Preferred in Formula IV are compounds wherein the dotted line represents no bond, particularly wherein D is CO or CHOH. More preferred are compounds wherein V is $-\text{CH} = \text{CH}-$, $-\text{CH} = \text{N}-$ or S and n is 2, particularly those compounds wherein X is O and Y is N, X is S and Y is N, X is S and Y is CH or X is $-\text{CH} = \text{N}-$ and Y is CH. In the most preferred compounds X is O or S and Y is N forming an oxazol-4-yl, oxazol-5-yl, thiazol-4-yl, or thiazol-5-yl group; most particularly a 2-[(2-thienyl), (2-furyl), phenyl, or substituted phenyl]-5-methyl-4-oxazolyl group.

The preferred compounds in Formula V are:

- a) those wherein the dotted line represents no bond, A and B are each CH, X_1 is CO, n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2 or $\text{CH}=\text{CH}$ and X_3 is hydrogen, particularly when X_2 is hydrogen, 2-methoxy, 4-benzyloxy, or 4-phenyl;
- b) those wherein A and B are each CH, X_1 is S or SO_2 , n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2 and X_3 is hydrogen, particularly when X_2 is hydrogen or 4-chloro.

A preferred group of compounds is that of Formula VI wherein R_{23} is (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl, halophenyl, or (C_1-C_6) alkylphenyl. Especially preferred within this group are the compounds where R_{23} is phenyl, methylphenyl, fluoro-phenyl, chlorophenyl, or cyclohexyl.

When used herein with regard to Formulas VII through X, the term "aryl" includes phenyl and

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naphthyl, suitably phenyl, optionally substituted with up to 5, preferably up to 3, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term "halogen" refers to fluorine, chlorine, bromine, and iodine; preferably chlorine.

The terms "alkyl" and "alkoxy" relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

Suitable alkyl groups are C₁₋₁₂ alkyl groups, especially C₁₋₆ alkyl groups, e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of alkyl, alkoxy, aryl, and halogen or any 2 substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said 2 substituents may themselves be substituted or unsubstituted.

Specific examples of compounds of the present invention are given in the following list:

(+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl)methyl]-2,4-thiazolidinedione;

4-(2-naphthylmethyl)-1,2,3,5-oxathiadiazole-2-oxide;

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]-ethoxy]benzyl]-5-methylthiazolidine-2,4-dione;

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5-[4-[2-[2,4-dioxo-5-phenylthiazolidin-3-yl)-ethoxy]benzyl]thiazolidine-2,4-dione;

5-[4-[2-[N-methyl-N-(phenoxy-carbonyl)amino]-ethoxy]benzyl]thiazolidine-2,4-dione;

5 5-[4-(2-phenoxyethoxy)benzyl]thiazolidine-2,4-dione;

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione;

10 5-[4-[2-(4-chlorophenyl)ethylsulfonyl]benzyl]-thiazolidine-2,4-dione; and

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione.

As defined herein, "complications of NIDDM" is referred to as cardiovascular complications or several of the metabolic and circulatory disturbances that are associated with hyperglycemia, e.g., insulin resistance, hyperinsulinemia and/or hyperproinsulinemia, delayed insulin release, dyslipidemia, retinopathy, peripheral neuropathy, nephropathy, and hypertension.

The compounds of Formulas I through X are capable of further forming pharmaceutically acceptable base salts.

25 The compounds of Formulas I through X are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I through X include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids,

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aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glucamine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner or as above. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see,

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for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

5 The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional
10 manner or as above. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present
15 invention.

 Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are
20 equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

 Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in different configurations. The compounds can, therefore, form stereoisomers. Although these are all represented herein by a limited number of molecular
25 formulas, the present invention includes the use of both the individual, isolated isomers and mixtures, including racemates, thereof. Where stereospecific
30 synthesis techniques are employed or optically active compounds are employed as starting materials in the preparation of the compounds, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be
35 obtained by conventional resolution techniques, or the mixture may be used as it is, without resolution.

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Furthermore, the thiazolidene part of the compound of Formulas I through X can exist in the form of tautomeric isomers. All of the tautomers are represented by Formulas I through X, and are intended to be a part of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

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For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package

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containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use in the treatment of at risk populations such as those with impaired glucose tolerance, to prevent or delay the onset of NIDDM and complications arising therefrom, the compounds utilized in the pharmaceutical methods of this invention are administered along with a pharmaceutically acceptable carrier at the initial dosage of about 0.01 mg to about 20 mg per kilogram daily. A daily dose range of about 0.01 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

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The compounds of Formulas I through X are valuable agents in returning an individual to a state of glucose tolerance and therefore preventing or delaying the onset of NIDDM. Tests were conducted which showed that compounds of Formulas I through X possess the disclosed activity. The tests employed on the compounds of Formulas I through X were performed by the following study.

EXAMPLE 1

A study will be performed to determine the effect of troglitazone ((+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl)methyl]-2,4-thiazolidinedione) on insulin resistance and androgen levels in PCOS women. Since hyperandrogenism results in chronic anovulation and hirsutism, decreasing androgen levels may improve hirsutism and even restore normal ovulatory menstrual function in PCOS women. The specific aim of the study will be to determine the effects of improved insulin sensitivity and decreased insulin levels secondary to troglitazone treatment on circulating androgen and gonadotropin levels in PCOS women.

I. SUBJECTS

A. General Selection Criteria. A total of 30 women will be studied. All subjects will be in excellent health, between the ages of 18-45 years, and euthyroid. There will be no history of cardiorespiratory, hepatic, or renal dysfunction. No subject will be taking any medications known to affect reproductive hormone levels or carbohydrate metabolism for at least 1 month prior to study, with the exception of oral contraceptives, which will be discontinued 3 months prior to study. Obesity will be defined as body mass index (BMI: $\text{wt (kg)/hr}^2\text{(m)}$ of $\geq 27 \text{ kg/m}^2$, non-obese patients will have a BMI of $\leq 25 \text{ kg/m}^2$.

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B. Selection criteria for PCOS. The diagnosis of PCOS will require biochemically documented hyperandrogenism (serum levels of testosterone, biologically available testosterone, and/or androstenedione two standard deviations or more above the control mean), chronic anovulation (<6 menses/year or dysfunctional uterine bleeding), and polycystic ovaries present on vaginal ovarian ultrasound. These are the least controversial criteria for diagnosis for PCOS. The LH:FSH ratio and hirsutism will not be used as selection criteria. Androgen secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia will be excluded by appropriate tests in all women. Women with hyperprolactinemia will be excluded because of the possible effect of hyperprolactinemia on insulin sensitivity.

C. Disqualification Criteria

1. Pregnancy
2. Intercurrent medical illness
3. Hepatic or renal dysfunction
4. Hemoglobin < 11 gm/dL
5. Weight < 50 kg.

II. STUDY PROTOCOL

A. Subject Preparation for All Studies. All testing will be performed during a period of documented anovulation by plasma progesterone levels in PCOS women. Subjects will consume a 55% carbohydrate, 30% fat, 15% protein weight maintaining diet for 3 days prior to testing and all testing will be done in the post-absorptive state after 10-12 hours fast.

B. Protocol

1. Visit 1 - Day 1. A complete history and physical examination will be performed and blood for a complete

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blood count, electrolytes, thyroid function (thyroid profile with TSH level), renal chemistries and liver function will be obtained. Blood for testosterone (T), biologically available T (uT), LH, FSH, dehydro-
 5 epiandrosterone sulfate (DHEAS), androstenedione (A), sex hormone binding globulin (SHBG), estrone (E₁), estradiol (E₂), insulin, and C-peptide levels will be obtained. A 75 g glucose load will be ingested in the morning after a 10-12 hr fast, and glucose and insulin
 10 levels will be obtained every 30 minutes for 2 hours. All PCOS women will have fasting insulin levels ≥ 15 μ U/mL and may have impaired glucose tolerance by WHO criteria. No subject, however, will have diabetes mellitus.

WHO Diagnostic Criteria

Serum Glucose mg/dL (mmol/L)	Normal	IGT	Diabetes
Fasting	<140 (<7.8)	<140 (<7.8)	≥ 140 (≥ 7.8)
2 hour	<140 (<7.8)	140-199 (7.8-11.1)	≥ 200 (≥ 11.1)

2. Visit 1 - Day 2. A frequently sampled intravenous glucose tolerance test (FSIGT) will be performed.

25 Basal blood samples will be collected at -15, -10, -5, and -1 minute. Glucose (300 mg/kg) will be injected as an IV bolus at time 0 minute and tolbutamide (500 mg) will be injected at 20 minutes. Blood samples will be taken at 2, 3, 4, 5, 8, 10, 12, 14, 16, 19, 22, 23, 24,
 30 25, 27, 30, 40, 50, 60, 70, 90, 100 minutes, and every 20 minutes thereafter until 240 minutes for glucose and insulin levels.

3. Troglitazone therapy. Troglitazone will be started after Visit 1, Day 2, when a urine pregnancy
 35 test will be documented to be negative. Troglitazone will be administered in a double-blind randomized trial of two dose levels: 200 mg/day and 400 mg/day. Subjects will be randomly assigned to one of the two

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daily doses of troglitazone. All women will take two pills: either two 200 mg pills or a 200 mg pill and a placebo pill. There will be 15 subjects in each of the two treatment groups. Troglitazone will be administered as a single daily dose with breakfast.

4. Visits 2 and 3. Subjects will return monthly. Blood will be obtained every 10 minutes x 3 and the plasma pooled for assay of T, μ T, A, DHEAS, SHBG, E_2 , E_1 , LH, and FSH levels. Insulin and glucose levels basally and 2 hours after 75 g glucose will be determined.

5. Visit 4. The studies performed at Visit 1 will be repeated. Subjects will be instructed to return all unused supplies or empty bottles at the time of each visit to ensure compliance. Details related to patient dosage and compliance will be recorded on the case report form.

III. STATISTICAL ANALYSIS

Each subject will serve as her own control, and the data will be analyzed by paired t-test. Differences in treatment vs baseline hormone levels and parameters of insulin action will be compared between the two dose groups by unpaired t-tests. Repeated measures of analysis of variance will be performed to determine changes over time. Log transformation of the data will be performed when necessary to achieve homogeneity of variance. This is a pilot study and 15 PCOS women each will be examined at two dose levels of troglitazone.

IV. HUMAN SUBJECTS

A. Risks

1. Blood Withdrawal. All subjects will have normal a complete blood count and hemoglobin levels >11 mg/dL.

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No subject will have >500 mL blood drawn in 24-hour period and >1000 mL blood drawn over 12-week period.

2. FSIGT. There is a small risk of hypoglycemia during FSIGT, and the test will be terminated

5 immediately by administration of 50% dextrose if signs or symptoms of severe hypoglycemia develop. There is a small risk of allergy to tolbutamide; the drug will not be given to any subject with a history of allergy to sulfa drugs or sulfonylureas.

10 3. Troglitazone. The major side effects of troglitazone are nausea, peripheral edema, and abnormal liver function. Other reported adverse events include dyspnea, headache, thirst, gastrointestinal distress, insomnia, dizziness, incoordination, confusion,
15 fatigue, pruritus, rash, alterations in blood cell counts, changes in serum lipids, acute renal insufficiency, and dryness of the mouth. Additional symptoms that have been reported, for which the relationship to troglitazone is unknown, include palpitations,
20 sensations of hot and cold, swelling of body parts, skin eruption, stroke, and hyperglycemia.

4. Disqualification Criteria. Subjects will be disqualified if they will develop one or more of the following: HB <11 gm/dL, wt <50 kg, abnormal hepatic
25 or renal chemistries, hypertension, pregnancy, significant illnesses, or excessive bleeding.

	History Physical	EKG	Pregnancy Test	Chemistry ^a	Hormones ^b	OGTT	FSIGT	Timing
Visit 1 - Day 1	X	X		X	X	X		Baseline
Visit 1 - Day 2			X				X	Baseline
Visit 2	X		X		X	X		1 month
Visit 3	X		X		X	X		2 months
Visit 4 - Day 1	X	X		X	X	X		3 months
Visit 4 - Day 2			X				X	3 months

^a Chemistry - Complete blood count with differential, electrolytes, liver function, renal function, thyroid profile with TSH level

^b Hormones - T, μ T, LH, FSH, DHEAS, SHBG, P, A, E₂, E₁, insulin, C-peptide levels

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EXAMPLE 2

Thiazolidinediones have been shown to increase insulin sensitivity in insulin-resistant, non-diabetic and diabetic animals and in humans with NIDDM. Several
5 thiazolidinediones are undergoing testing in the U.S., including studies of proglitazone in fructose-fed rats and obese rhesus monkeys. The drugs appear to improve insulin sensitivity in skeletal muscle and liver, major sites of insulin resistance in NIDDM. In response to
10 the increased insulin sensitivity, which has been in the range of 40-100% above pretreatment levels, pancreatic B-cells appear to down-regulate insulin secretion, so that hyperinsulinemia is reduced and hypoglycemia is not a risk. Of the possible
15 pharmacological interventions, thiazolidinediones appear well-suited for testing in the prevention of NIDDM in patients whose underlying insulin resistance is thought to lead to B-cell decompensation and diabetes. Therefore, it is proposed to test the effects of a
20 thiazolidinedione that has been shown to increase insulin sensitivity in people with NIDDM, on insulin sensitivity and NIDDM rates in our very high-risk patients with recent GDM.

In particular, it is proposed to test the effects
25 of the agent, troglitazone, that has been shown to enhance insulin-mediated glucose disposal in humans. While not wishing to be bound by theory, if the hypothesis is correct, troglitazone will maintain insulin action at a level which is commensurate with
30 B-cell reserve in some, and perhaps many subjects, thereby preventing or delaying the development of NIDDM.

The demonstration that treatment with troglitazone will reduce the rate of NIDDM in patients with GDM will
35 have important clinical and biological significance. The clinical significance is the obvious potential for

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treatment of GDM patients to prevent or delay overt diabetes and its long-term complications. The choice of an agent that improves insulin action may not only reduce the risk of diabetic complications that clearly are related to chronic metabolic decompensation (i.e., retinopathy, nephropathy, and neuropathy), but also may reduce the risk of cardiovascular complications such as hypertension and atherosclerosis, that have been associated with insulin resistance and hyperinsulinemia. The biological significance of a reduced rate of diabetes during treatment with troglitazone will depend to some extent on the effects of the drug on insulin action.

To test the hypothesis that interventions to improve whole-body insulin sensitivity will reduce the rate of B-cell decompensation and delay or prevent the development of NIDDM, a randomized, double-blind, placebo-controlled trial of troglitazone will be performed. The trial will be performed among individuals at high risk for NIDDM such as women with a history of GDM. In particular, because the age-adjusted prevalence rates of NIDDM among Hispanic women aged 24-64 years have been reported to be 8-11%, rates which are 2-3 times those of non-Hispanic whites in the U.S., the test will be performed among Hispanic women.

I. OVERVIEW OF STUDY DESIGN

Hypothesis: Troglitazone will improve insulin sensitivity and delay or prevent NIDDM in Latino women with a history of GDM who are at very high risk for NIDDM.

Patients: ~230 Hispanic women with recent GDM and a glucose tolerance test at 6-12 weeks postpartum indicating a very high risk of developing NIDDM within 3-5 years (i.e., total glucose area >16.3 gm·min/dL).

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Procedures:

1. Measure whole-body insulin sensitivity (minimal model S_1) at baseline.
2. Randomize to drug or placebo (double-blind design).
3. Measure insulin sensitivity after 4 and 24 months on treatment.
4. Follow for development of NIDDM:
 - a. Fasting glucose at 4-month intervals
 - b. Oral glucose tolerance test annually
 - c. Mean follow-up of 36 months.

Analysis:

1. Between group (drug and placebo) comparison of cumulative NIDDM rates using life table methods:
 - a) by intent-to-treat
 - b) by response-to-therapy.
2. Between group comparison of 4-month changes in S_1 using 2-group t-test; between group changes in S_1 over time using repeated measures ANOVA.
3. Within and between group analysis of factors associated with any reduction in NIDDM rate using Cox proportional hazards regression analysis.

II. INTERVENTION TRIAL: SUBJECT SELECTION AND ENROLLMENT**A. Inclusion and Exclusion Criteria**

- INCLUSION:** Age 18-45 years, recent GDM by the National Diabetes Data Group criteria, Diabetes, 29:1039-1057 (1979), singleton pregnancy, Mexican-American or Central-American (self-declared ethnicity); both parents and 3/4 grandparents of Mexican or Central American heritage, residence within 60 minutes of

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LAC Medical Center, 6-12 week postpartum OGTT glucose area >16.3 gm·min/dL.

EXCLUSION: Plans for pregnancy within 4 years, medical illness requiring chronic medications that
5 alter glucose tolerance or that will preclude 3-4 years of follow-up (e.g., malignancy, HIV infection), illicit drug abuse, inability to give informed consent.

III. SPECIFIC PROCEDURES

10 A. OGTT

1. Procedure: Sitting subjects will have an indwelling antecubital venous catheter placed in the morning after a 10-12 hour fast. At least 30 minutes later, dextrose (75 g) will be given orally over
15 5 minutes. Blood will be drawn at -10, 30, 60, 90, and 120 minutes from the start of the dextrose ingestion.

2. Interpretation: OGTTs plasma glucose concentrations will be interpreted according to National Diabetes Data Group criteria.

20 3. Risks: Limited to those of an intravenous line (pain, infection, bruising/bleeding at site), nausea at the time of dextrose ingestion, and phlebotomy (15 mL blood).

25 B. IVGTT

1. Procedure: After an overnight fast, subjects will be placed at bedrest and will have bilateral antecubital venous catheters placed. At least 30 minutes later, a basal blood sample will be drawn
30 and dextrose (300 mg/kg body weight) will be given intravenously over 1 minute. An intravenous injection of tolbutamide (3 mg/kg) will be given 20 minutes after the dextrose injection. Plasma samples will be
35 obtained at 2, 4, 8, 14, 19, 22, 30, 40, 50, 70, 100, and 180 minutes after the glucose injection and assayed for glucose and insulin.

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2. Analysis: Insulin sensitivity will be calculated by computer analysis of the glucose and insulin patterns during the IVGTT.

5 3. Risks: Hypoglycemia is a potential complication following tolbutamide injection. However, tolbutamide is injected when the plasma glucose is high, so that hypoglycemia is unusual. It has never been observed in over 50 IVGTTs in Hispanic women using the 3 mg/kg tolbutamide dose. Nonetheless, patients will be
10 observed for symptoms of hypoglycemia and stop the test if symptomatic hypoglycemia (<60 mg/dL) occurs. Risks of intravenous lines and phlebotomy (total = 39 mL) are minimal. Persons with a hematocrit $<33\%$ will not be studied with the IVGTT.

15

C. Body Morphometry

1. Procedures: Body weight will be measured on a standard beam balance (subjects lightly clothed, without shoes). Height will be measured with a
20 statometer. Waist circumference will be measured at the minimum circumference between the thorax and the iliac crest. Hip circumference will be measured at the level of the maximum posterior protrusion of the buttocks.

25 2. Interpretation: Body mass index will be calculated as: $[\text{weight in kg}]/[\text{height in meters}]$ and used as a surrogate for measures of adiposity. The ratio of the waist circumference to the hip circumference will be calculated as a measure of fat
30 distribution. Each measure will be tested as a predictive feature for NIDDM and for any effects of therapy on NIDDM risk.

3. Risks: None.

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D. Blood Pressure

Blood pressure will be measured in triplicate in sitting (\times 5 minutes) patients with an aerioid sphygmomanometer. First and fourth Korotkoff sounds will be used to determine systolic and diastolic BP. There are no risks associated with the procedure.

E. Assays

1. Insulin: Insulin is measured in plasma with a charcoal precipitation radioimmunoassay using human insulin standard, guinea pig anti-porcine insulin antibodies, and tyrosine A-19 iodoinsulin purchased from Novo-Nordisk. Quality control will be maintained. RIA has a mean interassay coefficient of variation of 12% at $7 \pm 3 \mu\text{U/mL}$ and 7% at $32 \pm 6 \mu\text{U/mL}$, based on pooled plasma samples stored at -70°C over a period of 12 months.

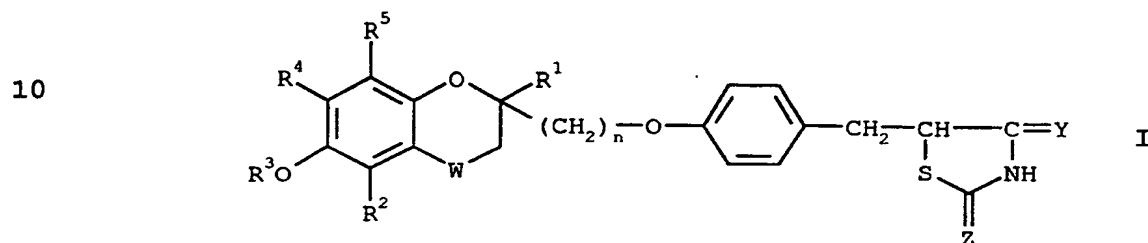
2. Glucose: Glucose will be measured in duplicate by glucose oxidase (Beckman Glucose Analyzer II).

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

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CLAIMS

1. A method of treating polycystic ovary syndrome or gestational diabetes in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I in unit dosage form:



- 15 wherein R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group;

- 20 R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1 - C_6 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

- 25 R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylendioxy group;
 n is 1, 2, or 3;

- 30 W represents the $-CH_2-$, $>CO$, or $CO-OR^6$ group (in which R^6 represents any 1 of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

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Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group; and pharmaceutically acceptable salts thereof.

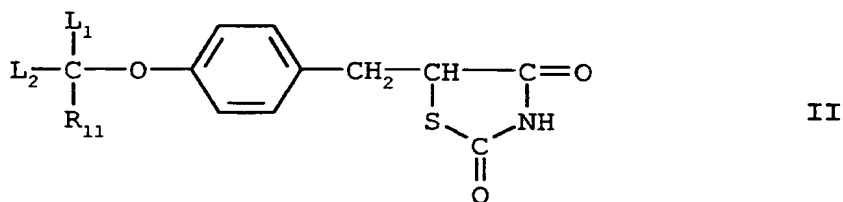
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2. A method of treating polycystic ovary syndrome or gestational diabetes in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
3. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein Y and Z are oxygen.
4. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein W is -CH₂-.
5. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein n is 1.
6. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein R₁, R₂, R₄, and R₅ are lower alkyl and R₃ is H.

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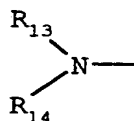
7. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein Z and Y are oxygen, n is 1, and W is -CH₂-.
8. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein the compound is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione.
9. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II in unit dosage form



wherein R₁₁ is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula

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20



25

wherein R₁₃ and R₁₄ are the same or different and each is lower alkyl or R₁₃ and R₁₄ are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring;

30

wherein R₁₂ means a bond or a lower alkylene group; and

35

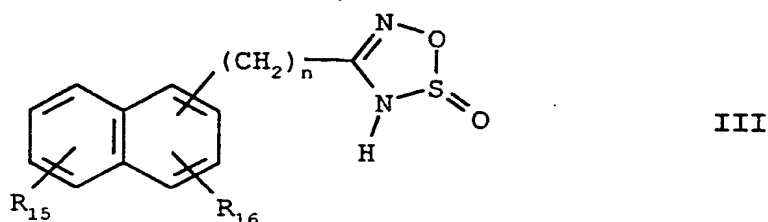
wherein L₁ and L₂ are the same or different and each is hydrogen or lower alkyl or L₁ and L₂ are combined to form an alkylene group, or a pharmaceutically acceptable salt thereof.

5

10. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering a therapeutically effective amount of a compound according to Claim 9 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
11. A method of Claim 10 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II wherein the compound is pioglitazone.
12. A method of Claim 10 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II wherein the compound is ciglitazone.

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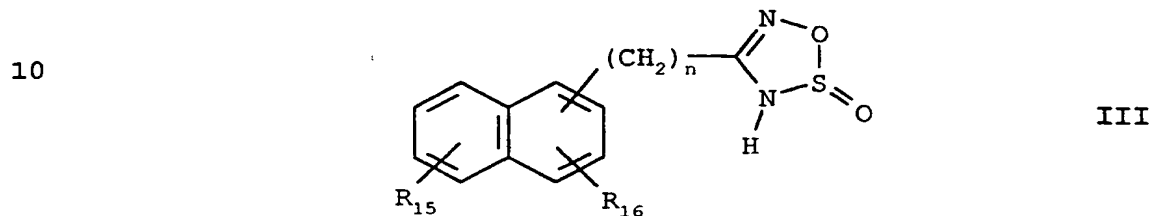
13. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula III in unit dosage form



15 wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

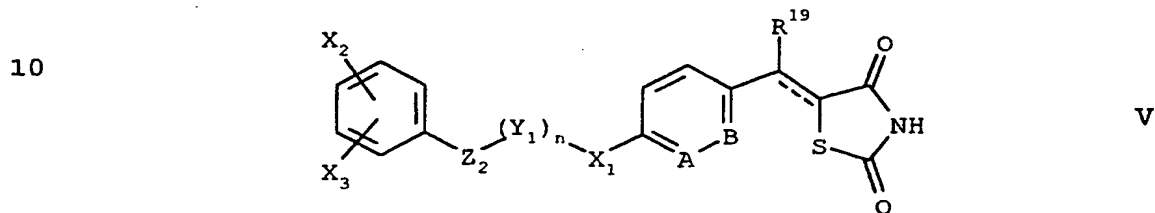
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14. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula IV in unit dosage form



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- 15 wherein the dotted line represents a bond or no bond;
 V is $-\text{CH} = \text{CH}-$, $-\text{N} = \text{CH}-$, $-\text{CH} = \text{N}-$ or S;
 D is CH_2 , CHOH , CO , $\text{C} = \text{NOR}_{17}$ or $\text{CH} = \text{CH}$;
 X is S, O, NR_{18} , $-\text{CH} = \text{N}$ or $-\text{N} = \text{CH}$;
 20 Y is CH or N;
 Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7) cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are (C_1-C_3) alkyl,
 25 trifluoromethyl, (C_1-C_3) alkoxy, fluoro, chloro, or bromo;
 Z' is hydrogen or (C_1-C_3) alkyl;
 R_{17} and R_{18} are each independently hydrogen or methyl; and n is 1, 2, or 3;
 30 the pharmaceutically acceptable cationic salts thereof; and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.
15. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula V in unit dosage form



- 15 wherein the dotted line represents a bond or no bond;

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A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;

X_1 is S, SO, SO₂, CH₂, CHOH, or CO;

20 n is 0 or 1;

Y_1 is CHR₂₀ or R₂₁, with the proviso that when n is 1 and Y_1 is NR₂₁, X_1 is SO₂ or CO;

25 Z_2 is CHR₂₂, CH₂CH₂, CH=CH, $\begin{array}{c} \text{CH}-\text{CH} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$, OCH₂,

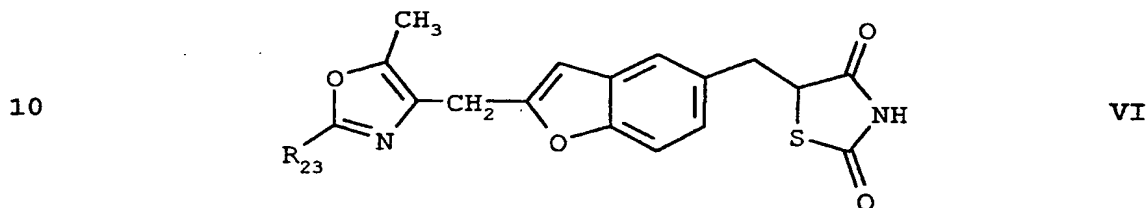
SCH₂, SOCH₂ or SO₂CH₂;

R₁₉, R₂₀, R₂₁, and R₂₂ are each independently hydrogen or methyl; and

30 X_2 and X_3 are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro; a pharmaceutically acceptable cationic salt thereof; or

35 a pharmaceutically acceptable acid addition salt thereof when A or B is N.

16. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula VI in unit dosage form

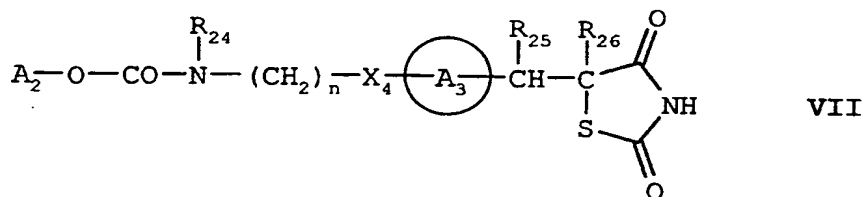


15 or a pharmaceutically acceptable salt thereof wherein R₂₃ is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, or

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mono- or disubstituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

17. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula VII in unit dosage form



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

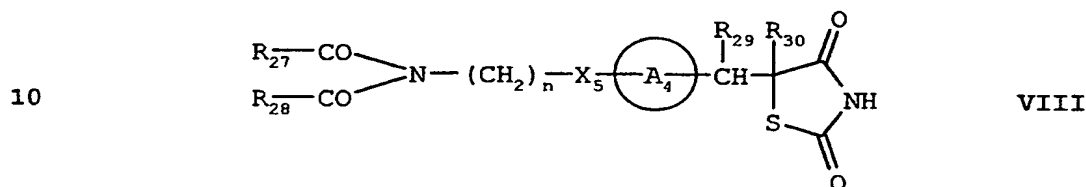
A_3 represents a benzene ring having in total up to 3 optional substituents;

R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl, or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or

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adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;
 35 R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;
 X_4 represents O or S; and
 n represents an integer in the range of from 2 to 6.

18. A method of treating polycystic ovary syndrome or gestational diabetes to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula VIII in unit dosage form



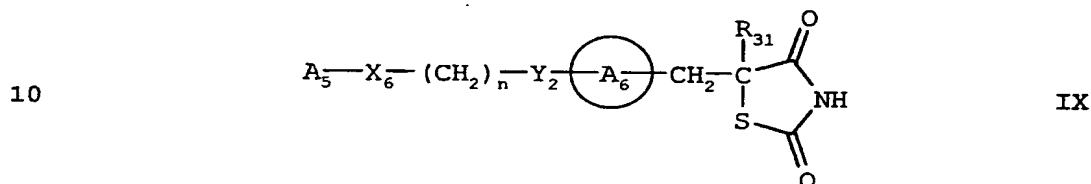
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety;
 20 or R_{27} together with R_{28} represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-,
 25

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30 aryl, or aralkyl, or substituents of adjacent
 methylene groups together with the carbon atoms to
 which they are attached form a substituted or
 unsubstituted phenylene group;
 R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30}
 together represent a bond;
 35 A_4 represents a benzene ring having in total up to
 3 optional substituents;
 X_5 represents O or S; and
 n represents an integer in the range of from
 2 to 6.

19. A method of treating polycystic ovary syndrome or
 gestational diabetes to prevent or delay the onset
 of noninsulin-dependent diabetes mellitus
 comprising administering to a host suffering
 5 therefrom a therapeutically effective amount of a
 compound of Formula IX in unit dosage form



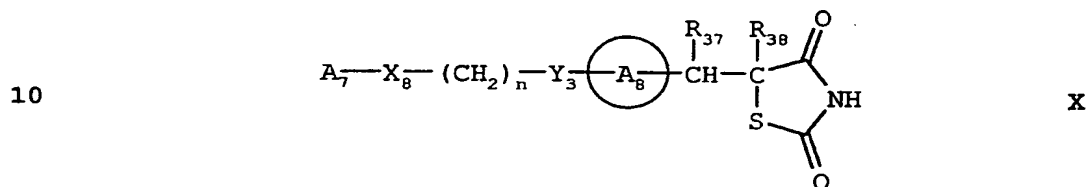
15 or a tautomeric form thereof and/or a
 pharmaceutically acceptable salt thereof, and/or a
 pharmaceutically acceptable solvate thereof,
 wherein:

20 A_5 represents a substituted or unsubstituted
 aromatic heterocyclyl group;
 A_6 represents a benzene ring having in total up to
 5 substituents;
 X_6 represents O, S, or NR_{32} wherein R_{32} represents
 a hydrogen atom, an alkyl group, an acyl group, an
 aralkyl group, wherein the aryl moiety may be

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25 substituted or unsubstituted, or a substituted or
 unsubstituted aryl group;
 Y_2 represents O or S;
 R_{31} represents an alkyl, aralkyl, or aryl group;
 and
 30 n represents an integer in the range of from
 2 to 6.

20. A method of treating polycystic ovary syndrome or
 gestational diabetes to prevent or delay the onset
 of noninsulin-dependent diabetes mellitus
 comprising administering to a host suffering
 5 therefrom a therapeutically effective amount of a
 compound of Formula X in unit dosage form



15 or a tautomeric form thereof and/or a pharmaceu-
 tically acceptable salt thereof, and/or a
 pharmaceutically acceptable solvate thereof,
 wherein:

A_7 represents a substituted or unsubstituted aryl
 group;
 20 A_8 represents a benzene ring having in total up to
 5 substituents;
 X_8 represents O, S, or NR_{39} , wherein R_{39} represents
 a hydrogen atom, an alkyl group, an acyl group, an
 aralkyl group, wherein the aryl moiety may be
 25 substituted or unsubstituted, or a substituted or
 unsubstituted aryl group;
 Y_3 represents O or S;
 R_{37} represents hydrogen;

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R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and n represents an integer in the range of from 2 to 6.

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(57) Abstract Novel methods of using thiazolidinone derivatives and related antihyperglycemic agents to treat populations at risk for developing noninsulin-dependent diabetes mellitus (NIDDM) and complications arising therefrom are disclosed. In one embodiment, the compounds of the invention are used to treat polycystic ovary syndrome in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus. In another embodiment, the compounds of the invention are used to treat gestational diabetes in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus.		

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CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/10187

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/425 A61K31/44 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 139 421 (SANKYO) 2 May 1985 cited in the application & US,A,4 572 912 (YOSHIOKA ET AL.) see abstract see page 1, line 15 - page 2, line 3 see page 81, line 19 - line 22; claims ---	1-8
X	EP,A,0 008 203 (TAKEDA) 20 February 1980 cited in the application & US,A,4 287 200 (YUTAKA ET AL.) see abstract; claims; examples ---	9,10,12
X	EP,A,0 332 332 (PFIZER) 13 September 1989 see abstract see page 9, line 33 - page 10, line 3; claims --- -/--	14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 December 1994

Date of mailing of the international search report

18. 04. 95

Name and mailing address of the ISA

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Authorized officer

HOFF, P

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 94/10187

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 332 331 (PFIZER) 13 September 1989 cited in the application see abstract see page 9, line 9 - line 30; claims & US,A,5 223 522 (CLARK ET AL.) ---	15
X	WO,A,93 00343 (PFIZER) 7 January 1993 see abstract see page 14, line 6 - page 15, line 7; claims ---	16
X	WO,A,92 07838 (BEECHAM) 14 May 1992 see abstract see page 1, line 15 - line 19; claims ---	17
X	WO,A,92 07839 (BEECHAM) 14 May 1992 see abstract see page 1, line 16 - line 21; claims ---	18
X	EP,A,0 419 035 (BEECHAM) 27 March 1991 see abstract see page 3, line 8 - line 10; claims ---	19
X	EP,A,0 415 605 (BEECHAM) 6 March 1991 cited in the application see abstract see page 2, line 8 - line 10; claims & US,A,5 132 317 (CANTELLO ET AL.) ---	20
X	DIABETES CARE, vol.15, no.8, 1992 pages 1075 - 1078 C.A. HOFMAN ET AL. 'NEW ORAL THIAZOLIDINEDIONE ANTIDIABETIC AGENTS ACT AS INSULIN SENSITIZERS' see the whole document ---	1-11
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.14, 1992 pages 2617 - 2626 T. SOHDA ET AL. 'STUDIES ON ANTIDIABETIC AGENTS' see the whole document ---	9-12
X	CHEMICAL ABSTRACTS, vol. 119, no. 1, 5 July 1993, Columbus, Ohio, US; abstract no. 97, 'CS-045, AN AMELIORATOR FOR INSULIN RESISTANCE' see abstract & DIABETES FRONT., vol.3, no.6, 1992 pages 570 - 574 KANAZAWA ET AL. --- -/--	1-8

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/10187

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol.687, May 1993 pages 60 - 64 A. DUNAIF 'INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYNDROME' see the whole document ---	1-20
A	ANNALES D'ENDOCRINOLOGIE, vol.53, no.1, 1992 pages 1 - 7 D. DEWAILLY ET AL. 'INSULINORESISTANCE ET SYNDROME DES OVAIRES POLYMICROKYSTIQUES' see the whole document ---	1-20
A	DIABETOLOGIA, vol.34, 1991 page A198 S. ROBINSON ET AL. 'INSULIN RESISTANCE IS AN EARLY FEATURE OF GESTATIONAL DIABETES' see the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/10187

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 1-12, 14-20 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The structure of claim 14 doesn't correspond to the formula IV described page 11 line 14-35. The search was based on the structure defined in the description page 11 (formula IV).
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see annex.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12, 14-20

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US94/ 10187

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Continuation of BOX II:

1. Claims: 1-12,14-20 Method for treating polycystic ovary syndrome or gestational diabetes with thiazolidine derivatives. The structure of claim 14 has been considered as the structure IV described page 11 line 14-35.
2. Claim : 13 Method for treating polycystic ovary syndrome or gestational diabetes with oncathiadiazole derivatives.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/10187

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0139421	02-05-85	JP-C- 1604002	22-04-91
		JP-B- 2031079	11-07-90
		JP-A- 60051189	22-03-85
		AU-B- 570067	03-03-88
		AU-A- 3255984	07-03-85
		CA-A- 1263395	28-11-89
		DE-A- 3470742	01-06-88
		IE-B- 58036	16-06-93
		US-A- 4572912	25-02-86
US-A-4572912	25-02-86	JP-C- 1604002	22-04-91
		JP-B- 2031079	11-07-90
		JP-A- 60051189	22-03-85
		AU-B- 570067	03-03-88
		AU-A- 3255984	07-03-85
		CA-A- 1263395	28-11-89
		DE-A- 3470742	01-06-88
		EP-A, B 0139421	02-05-85
		IE-B- 58036	16-06-93
EP-A-0008203	20-02-80	JP-C- 1433701	07-04-88
		JP-A- 55022636	18-02-80
		JP-B- 62042903	10-09-87
		CA-A- 1131644	14-09-82
		US-A- 4287200	01-09-81
		US-A- 4340605	20-07-82
		US-A- 4438141	20-03-84
		US-A- 4444779	24-04-84
US-A-4287200	01-09-81	JP-C- 1433701	07-04-88
		JP-A- 55022636	18-02-80
		JP-B- 62042903	10-09-87
		CA-A- 1131644	14-09-82
		EP-A, B 0008203	20-02-80
		US-A- 4340605	20-07-82
		US-A- 4438141	20-03-84
		US-A- 4444779	24-04-84
EP-A-0332332	13-09-89	WO-A- 8908651	21-09-89
		CA-A- 1328873	26-04-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/10187

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0332332		ES-T- 2053977 FI-B- 93115 PT-B- 89912 US-A- 5130379	01-08-94 15-11-94 31-05-94 14-07-92
EP-A-0332331	13-09-89	WO-A- 8908650 CA-A- 1328872 DE-D- 68912952 DE-T- 68912952 PT-B- 89913 US-A- 5061717 US-A- 5120754 US-A- 5223522	21-09-89 26-04-94 24-03-94 11-05-94 31-05-94 29-10-91 09-06-92 29-06-93
US-A-5223522	29-06-93	WO-A- 8908650 US-A- 5120754 CA-A- 1328872 DE-D- 68912952 DE-T- 68912952 EP-A- 0332331 PT-B- 89913 US-A- 5061717	21-09-89 09-06-92 26-04-94 24-03-94 11-05-94 13-09-89 31-05-94 29-10-91
WO-A-9300343	07-01-93	CA-A- 2111096 EP-A- 0591252 JP-T- 6503353	07-01-93 13-04-94 14-04-94
WO-A-9207838	14-05-92	AU-A- 8734791 EP-A- 0555251 JP-T- 6502145	26-05-92 18-08-93 10-03-94
WO-A-9207839	14-05-92	AU-B- 650296 AU-A- 8734591 CA-A- 2095146 EP-A- 0555249 JP-T- 6502146	16-06-94 26-05-92 01-05-92 18-08-93 10-03-94
EP-A-0419035	27-03-91	AT-T- 118487 DE-D- 69016899 JP-A- 3090078	15-03-95 23-03-95 16-04-91

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/10187

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0415605	06-03-91	AU-A- 6128590 DE-D- 69006984 DE-T- 69006984 JP-A- 3090071 US-A- 5132317	28-02-91 07-04-94 09-06-94 16-04-91 21-07-92
US-A-5132317	21-07-92	AU-A- 6128590 DE-D- 69006984 DE-T- 69006984 EP-A- 0415605 JP-A- 3090071	28-02-91 07-04-94 09-06-94 06-03-91 16-04-91